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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,572	11/30/2007	Gregory M. Lanza	532512001400	8304

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EXAMINER	
SHOMER, ISAAC	
ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,572	LANZA ET AL.	
	Examiner	Art Unit	
	ISAAC SHOMER	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *11-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10 November 2006, 8 August 2007, 25 November 2008, 11 June 2009*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions - Groups

Applicant's election with traverse of Group I, claims 1-10 in the reply filed on 15 October 2009 is acknowledged. The traversal is on the ground(s) that there is no lack of unity because the special technical feature of Group I does not lack novelty based upon the disclosure of Ahmad et al. (*Cancer Res.,* 1993, Vol. 53, pp. 1484-1488). However, this is not found persuasive because there is lack of unity between Groups I-VII as these inventions lack a shared special technical feature.

The special technical feature of Group I, claims 1-10, is a method of administering an active agent and an inactive carrier. The special technical feature of Group II, claims 11-21 is a composition wherein an active agent and an inactive carrier are in a single composition. As such a single composition is not specifically disclosed in instant claim 1, the special technical feature of Groups I and II is not shared, and there fore there is lack of unity. The special technical feature of Group III is a method of obtaining an ultrasound image. None of Groups I, II, and IV-VII are drawn to obtaining an ultrasound image. The special technical feature of Group IV is a method of obtaining a proton magnetic resonance image. None of Groups I-III and V-VII are drawn to obtaining a proton magnetic resonance image. The special technical feature of Group V is a method of obtaining an optical. None of Groups I-IV, VI, and VII are drawn to obtaining an optical image. The special technical feature of Group VI is a method of

obtaining an x-ray image. None of Groups I-V and VII are drawn to obtaining an x-ray image. The special technical feature of Group VII is a method of obtaining a F-19 magnetic resonance image. None of Groups I-VI are drawn to obtaining a F-19 magnetic resonance image. Therefore, there is no special technical feature shared between Groups I-VII.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 15 October 2009.

Election/Restrictions - Species

Applicant's election of the following species in the reply filed on 15 October 2009 is acknowledged:

Halocarbon-Hydrocarbon nanoparticles:

A binding moiety which is a peptidomimetic:

A binding target of alpha-v-beta-3:

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "substantially simultaneously" in claim 1 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See MPEP 2173.05(b)(D).

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Where values can vary depending on the basis for their determination, the claimed subject matter may be indefinite. *See* Honeywell Intl. v. Intl. Trade Commn., 341 F.3d 1332, 1340 (Fed. Cir. 2003). (Holding that, where a claimed value varies with its method of measurement and several alternative methods of measurement are available, the value is indefinite when the claim fails to concurrently recite the method of measurement used to obtain it). Accordingly, the limitation "the carrier of (2)" is "comprised of vehicles that are not of the same composition" recited by instant claim 7 is incomplete insofar as they do not specify the frame of reference used to measure them. For example, applicant's recitation of the term "composition" in the

second phrase is indefinite because it is unclear which composition is being recited. As such, it is unclear with what the comparison is being made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kao et al. (Biochimica et Biophysica Acta, Vol. 677, 1981, pp. 453-461) in view of Lanza et al. (Circulation, November 26, 200, pp. 2842-2847) and Lanza et al. (US 2002/0168320 A1).

Kao teaches that liposomes,[1] which are widely attractive for drug delivery (Kao, page 453 left column, top of first paragraph) suffer from extensive nonspecific uptake by phagocytes of the reticuloendothelial system (hereafter referred to as "RES"), as of Kao page 453 right column, bottom of page and onto page 454, wherein said RES clearance resembles that of colloid particles, as of Kao, page 454 left column, top of second full paragraph. Kao suggests reducing the rate of clearance by "blockade" of the RES, wherein large doses of colloid are administered for the purposes of saturating the uptake capacities of the RES, as of Kao, page 454 left column, second full paragraph. Kao conducts an experiment wherein C-14 labeled liposomes are given simultaneously with unlabeled liposomes, and the clearance time of the labeled liposomes are measured as a function of the concentration of unlabeled liposome, as of Kao, page 455 right column, section entitled "Blockade of REV Clearance by REVs" and onto the next page. Kao teaches that a small amount of blocking liposomes results in an acceleration in the clearance rate, whereas a large amount of blocking liposomes results in a reduction of the rate of liposome clearance, as of Kao, page 455 right column, last two lines, and page 456 right column, first two lines. Embodiments are taught wherein the

labeled and unlabeled particles are identical with the exception of the label (Kao, page 455 right column, “Blockade of REV clearance by REVs”) as well as non-identical (Kao, page 457 right column, "Blockade of REV clearance by SUVs.”). Kao, page 457 left column, Figure 3, teaches the use of 4 mg of labeled liposomes to 63 mg of unlabeled liposomes, indicating a carrier dose that exceeds that of the labeled composition.

Kao does not teach halocarbon/hydrocarbon nanoparticles and does not teach targeted particles.

Lanza et al. (Circulation, November 26, 2000, pp. 2842-2847) (hereafter referred to as Lanza) teaches the preparation of perfluorooctylbromide nanoparticles of about 250 nm (Lanza, page 2843 left column, first full paragraph) attached to targeting antibodies for the purpose of drug delivery of doxorubicin (Lanza, page 2843 right column last paragraph). Lanza indicates that targeted particle delivery results in greater cell death than untargeted particle delivery, as of Lanza, page 2844 right column Figure 3. Use of said particles as MRI contrast agents is also contemplated, as of Lanza, page 2844 right column bottom paragraph. Lanza teaches that the nanoparticles are constructed with biotin, as of Lanza, page 2843 left column, first full paragraph, and the method of treatment also comprises the use of avidin, as of Lanza, page 2844 left column, first paragraph in “VSMC Proliferation Assays” section.

Lanza et al. (US 2002/0168320 A1) (hereafter referred to as the ‘320 document) teaches that the presence of particles with avidin-biotin crosslinks promotes clearance via the reticuloendothelial system, as of paragraph 0031 of the '320 document.

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[1] Large unilamellar liposomes, known by Kao as REVs, are taught by Kao, page 453, bottom of left

It would have been prima facie obvious for one of ordinary skill in the art to have utilized the method of Kao for the purpose of drug delivery targeted perfluorooctyl bromide nanoparticles, as of Lanza. This is because one of ordinary skill in the art would have expected that the particles of Lanza would have been vulnerable to RES clearance, as taught by the '320 document. Therefore, one of ordinary skill in the art would have been motivated to have administered inactive particles with the active particles for the purpose of RES blockade using the method taught by Kao.

Kao, Lanza, and the '320 document do not appear to teach a method of administration wherein the dose of the blockade vehicles is 100 times greater than that of the labeled vehicles, as of claim 3.

Kao, page 457 left column, Figure 3, teaches the use of 4 mg of labeled liposomes to 63 mg of unlabeled liposomes, indicating a carrier dose that exceeds that of the labeled composition. However, it would have been prima facie obvious for one of ordinary skill in the art to have used an even higher ratio than that tested by Kao (at least 100:1). This determination is made in light of Kao, which teaches that a small amount of blocking liposomes results in an acceleration in the clearance rate, whereas a large amount of blocking liposomes results in a reduction of the rate of liposome clearance, as of Kao, page 455 right column, last two lines, and page 456 right column, first two lines. In view of the trend and relationship disclosed by Kao, one of ordinary skill in the art would have been motivated to have increased the loading ratio of

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column. The term liposome will be used in this action to refer to both small and large vesicles.

unlabeled liposomes to labeled liposomes to have achieved a more effective blockade of REV clearance.

Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kao et al. (Biochimica et Biophysica Acta, Vol. 677, 1981, pp. 453-461) in view of Lanza et al. (Circulation, November 26, 200, pp. 2842-2847) and Lanza et al. (US 2002/0168320 A1) as applied to claims 1-8 above, and further in view of Kerr et al. (Expern Opinion on Investigational Drugs, 2000, 9(6), pp. 1271-1279).

Kao in view of Lanza and the '320 document describe a method of administering targeted perfluorocarbon nanoparticles by co-administration of an inactive dose for the purpose of RES blockade. See supra rejection. Lanza encapsulated doxorubicin (Lanza, page 2843 right column last paragraph), and showed that targeted particle delivery results in greater cell death than untargeted particle delivery, as of Lanza, page 2844 right column Figure 3, indicating treatment of cell proliferation diseases such as cancer.

Kao in view of Lanza and the '320 document do not describe a peptidomimetic targeting ligand that targets the integrin alpha-v-beta-3 (hereafter AVB3) receptor.

Kerr et al. (hereafter referred to as Kerr) teaches that the integrin AVB3 is over-expressed on tumor cells as compared to normal cells, as of Kerr, page 1272 last full paragraph. Peptidomimetics for integrin AVB3 are contemplated on page 1274 left

column, first full paragraph. Use of AVB3 antagonists to deliver technetium-99 for imaging is described on Kerr, page 1274 right column second paragraph.

It would have been prima facie obvious for one of ordinary skill in the art to have used a peptidomimetic which targets integrin AVB3 on the fluorinated nanoparticles of Lanza. This is because said AVB3 is found primarily on cancer cells, and particles targeting AVB3 have been described to be suitable in cancer imaging, as of Kerr. As Lanza is drawn to delivery of anti-cancer drugs and to imaging, one of ordinary skill in the art would have been motivated to have used a peptidomimetic targeting AVB3 as the targeting agent of Lanza. Generally, it is *prima facie* obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended use. See MPEP 2144.07.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/I. S./
Examiner, Art Unit 1612

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612